Rejections under 35 USC 103

Claims 1-46 stand rejected as obvious over Gray or Buechler in view of Kucherlapati and Lonberg. Gray and Buechler are cited as teaching methods of phage display. The Examiner says that these references do not teach obtaining antibody sequences from a transgenic mouse or that libraries of human antibodies having affinities in excess of 10^9 M^{-1} were obtainable. Kucherlapati is cited as teaching a Xenomouse expressing human immunoglobulin genes. Kucherlapati is also cited as teaching that the combination of phage display technology with the Xenomouse offers a significant advantage over previous applications of phage display in obtaining high affinity human antibodies (citing to p. 13, lines 1-7). Lonberg is cited as teaching another example of a transgenic mouse. The Examiner takes the view that it would have been obvious to combine the teachings of the reference in view of Kucherlapati's teaching that the combination off phage display technology with a Xenomouse offers significant advantage over previous applications of phage display for obtaining high affinity antibodies (e.g., those with 10^9 M^{-1} or 10^{10} M^{-1} affinity).

In the previous response, applicants amended claim 1 to specify a population of at least 100 members at least 50% of which have an affinity of at least 10^9 M^{-1} . The feasibility of generating such a library is shown by the Table at p. 75 showing affinities in that the 10^{10}-10^{11} M^{-1} range, and p. 65, lines 19-29 showing that a high proportion of antibodies that were tested have such affinities. Applicants also noted that the success of the presently claimed methods in providing virtually unlimited numbers of high affinity human antibodies is a surprising result viewed from the perspective that generation of human antibodies with high affinity has long been viewed as a difficult task. Applicants also discussed at length why the cited Kucherlapati reference did not provide a reasonable expectation of success.

The Examiner now disagrees with applicants' position for three reasons. First, the Examiner says that nonobviousness cannot be shown by attacking the teaching of one reference alone when the rejection is based on a combination of references. Second, the Examiner says that the references do predict a reasonable expectation of success in view

of Kucherlapati's teaching in Table 4 that human antibodies with affinities ranging from 10^9 to $10^{11}M^{-1}$ can be obtained from a Xenomouse, Kucherlapati's further alleged teaching that combination of the Xenomouse with phage display offers significant advantage over previous applications of phase display in obtaining high affinity antibodies to human proteins, and a claim in Lonberg referring to a human antibody with a binding affinity of 10^{10} M^{-1}. Third, the Examiner says that applicants' remarks regarding potential loss of high affinity antibodies resulting from random assortment of heavy and light chains are countered by Burton's observation of antibodies with affinity constants of greater than 10^8M^{-1} using the phage display technique. This rejection is respectfully traversed. The Examiner's reasons are addressed in turn.

Applicants maintain that the previous comments on deficiencies in Kucherlapti's teaching provided a bona fide basis for withdrawing the rejection. When a rejection is based on reference A teaching X and reference B teaching Y, applicants would agree with the Examiner that it is useless to argue that reference A does not teach Y. However, if reference A does not teach X, then whether reference B teaches Y is immaterial, and the rejection collapses due to the deficiencies of reference A alone. This was essentially applicants' position in the last response.

The Examiner's principal basis that the references provide a reasonable expectation of success is Kucherlapati's alleged teaching that combination of the Xenomouse with phage display offers significant advantage over previous applications of phage display. However, as pointed out in the last response, the Examiner has taken this statement out of context. Although Kucherlapati does indicate that combination of phage display with the Xenomouse may be advantageous over previous applications of phage display, the advantage he identifies is that of extending the application of phage display to generation of human antibodies to human antigens (pp. 12-13). As Kucherlapati explains, phage display has been successfully used by others such as Burton et al. to generate moderate affinity antibodies (ca. 10^8 M^{-1}) to nonhuman antigens such as HIV, but has been much less successful in generating human antibodies to human antigens because of the inability to use such antigens as immunogens in a human. According to

Kucherlapati, use of the Xenomouse would allow one to immunize with a human antigen, and thereby presumably use phage display to obtain human antibodies to the human antigen in similar fashion to that employed by Burton to generate human antibodies to HIV. Kucherlapati does not say, however, that combination of the Xenomouse with phage display would allow one to generate higher affinity human antibodies to a human antigen than one could generate to a nonhuman antigen without a Xenomouse, such as described by Burton. The Examiner is thus taking Kucherlapati's comment on the advantage of combining phage display with the Xenomouse out of the context in which it was made, and overgeneralizing it into a general advantage of antibodies prepared using a combination of phage display and the Xenomouse to antibodies made using the Xenomouse alone.

The Examiner also refers to Table 4 of Kucherlapati apparently as disclosing examples of the high affinity human antibodies that might be generated by the combination of phage display and a transgenic mouse. However, the Examiner ignores the fact that the antibodies referred to in Table 4 were not generated by a combination of phage display and a transgenic mouse but using a transgenic mouse alone. As discussed in the last response, the natural pairings of heavy and light chain which are represented in antibodies isolated directly from a Xenomouse are likely to be lost during phage display. Thus, antibodies isolated using a combination of phage display and a Xenomouse would not necessarily be expected to have similar affinities to those isolated from the Xenomouse directly. In addition, Kucherlapati provides no indication of how many antibodies he had to screen to obtain the few high affinity antibodies shown in Table 4 of Kucherlapati. Thus, it is not at all apparent that Kucherlapati was able to isolate high affinity human antibodies at high frequency directly from the Xenomouse in contrast to the presently claimed methods.

For these reasons, it is not reasonably predictable from the Kurcherlapati reference that one could combine phage display and a transgenic mouse to generate the claimed populations of high affinity human antibodies.

The Examiner also refers to Burton's observation of antibodies with affinity constants of greater than 10^8M^{-1} using the phage display technique as rebutting applicants' position that random assortment of heavy and light chains might be expected to lower the affinity of antibodies attainable by combining phage display with a transgenic mouse. However, in fact, Burton's observations are consistent with applicants' position. As the Examiner has noted most of Burton's selected antibodies were in the 10^8 M^{-1} affinity range and only one reached 10^9 M^{-1}. This is considerably below the present claim requirement for at library of at least 100 members at least 50% of which comprising nucleic acids encoding human antibody chains having at least 10^9 M^{-1} affinity. Thus, Burton does not provide a reasonable expectation of success that the populations of antibodies of the present claims can be achieved.

The Examiner also refers to a claim in Lonberg as specifying a human antibody produced from a transgenic mouse with an affinity of 10^{10} M^{-1}. However, it is not disputed that antibodies having such affinities can be produced directly from transgenic mice. What is at issue is the frequency of representation of such antibodies both as directly isolated from a transgenic mouse, and when isolated by combining phage display with a transgenic mouse when the additional variable of random assortment of heavy and light chains occurs. As was noted in connection with Table 4 of Kucherlapati, Kucherlapati does not indicate the representation of high affinity human antibodies obtainable directly from a transgenic mouse, much less whether this representation is maintained notwithstanding the effects of random assortment of heavy and light chains. The Examiner has not identified what teaching in Lonberg compensates for this deficiency in Kucherlapati.

The Examiner also refers to Gray or Beuchler as disclosing antibody libraries having affinity of 10^{10} M^{-1}. However, these references do not provide data showing the affinity of human antibodies that can be isolated from a transgenic mouse using phage display or otherwise.

For these reasons, it is submitted that the other cited references do not cure any the deficiencies in Kucherlapti described in the last response and summarized above.

Claim 46

Claim 46 specifies methods in which nucleic acids from a transgenic mouse comprising less than the full complement of human immunoglobulin genes are amplified using a primer set selected based on which genes from the full complement are present in the transgenic mouse. Applicants previously pointed out that Kucherlapati takes a different approach in teaching that antibody chains be amplified using the primer set disclosed by Marks et al. , J. Mol. Biol. 581-596 (1991) (see Kucherlapati at p. 13, lines 7-9). The Marks reference is directed to use of phage display to screen antibody sequences from an unimmunized human. Marks' primer sets contain far fewer primers than there are natural immunoglobulin genes. Therefore, Marks probably selected his primers either from certain representative immunoglobulin sequences or from consensus sequences of different immunoglobulins. Applicants also described how use of Marks' primers would result in different amplified antibody sequences due to lack of complementarity or introduction of mutations.

The Examiner now says that applicants have not identified any objective evidence why one would have limited Kucherlapati's teaching to the use of Mark's primers. The Examiner also says that it would have been obvious and within the scope of skill of the artisan to design a set of primers selected based on which human immunoglobulin genes from the full complement of human immunoglobulins. The Examiner also says that Gray already shows that a library of replicable genetic packages containing members encoding antibodies with high binding affinity can be obtained without using customized primers of the present claims. The Examiner also says that the claims do not recite any characteristics of the customized primers that yield unexpected results as asserted by applicants. These points will be addressed in turn.

Insofar as the Examiner looks to applicants to identify negative teaching in the reference regarding using primers other than Marks, he is incorrectly transferring the PTO's burden of proof to applicants. In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a prima facie case of obviousness

based upon the prior art (*In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984)).. Although teaching away evidence may be sufficient for patentability, it is not necessary. The burden is on the Examiner to show that the reference discloses or suggests use of the customized primer sets specified in claim 46, not for applicants to identify negative or teaching away evidence. Here, Marks' primer sets are the only primers mentioned by Kucherlapati. Kucherlapati does not provide any reason that one would want to consider any other primers or even that this issue is worthy of further consideration. In these circumstances, it is submitted that the Examiner cannot fulfill the PTO's burden of showing that Kucherlapati suggests using primers other than those of Marks.

Next the Examiner alleges that it was within the skill of the art to design customized primer sets as claimed. However, even if true, this does not mean it was obvious to do so. A patentable invention may lie in the discovery of a source of a problem even though the remedy may be obvious once the source of a problem is identified. *In re Sponnobel*, 160 USPQ 237 (CCPA 1969). Here, the source of the problem is that using Marks primers will result in lack of amplification or misincorporation of some antibody chains, thereby potentially lowering the frequency of representation of high affinity antibodies in an amplified population. The Examiner has not identified where this information is identified in the cited art.

Next the Examiner alleges that Kucherlapati's teaching is compensated by one of the other cited references. However, none of the other cited references discuss combining phage display with transgenic animals, much less consider what primers to use for this purpose. Thus, the deficiencies of Kucherlapati are not compensated by the other cited references.

Finally, the Examiner says the claims do not recite any characteristics of the customized primers that yield unexpected results as asserted by applicants. However, applicants' position regarding claim 46 is not dependent on a showing of unexpected results. Rather the position is that the Examiner has not shown that the cited references disclose or suggest using a customized primer set for use in the claimed methods.

For all of these reasons, withdrawal of the rejection is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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